

Short-course itraconazole in the treatment of candida vulvovaginitis: A multicentre Canadian study

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OBJECTIVE: To determine the clinical and mycological effectiveness of oral itraconazole in the treatment of acute candida vulvovaginitis.

DESIGN: A prospective, randomized and single-blinded, multicentre trial of 221 women, comparing a one-day course of oral itraconazole 200 mg bid with vaginal clotrimazole 500 mg single-dose therapy.

MAIN OUTCOME MEASURES: Symptoms, signs and mycological results were assessed up to two months following treatment. Adverse events were recorded and evidence of hepatotoxicity sought.

RESULTS: At 10 and 30 days post-treatment, clinical and mycological cure rates were similar (61.3% clinical and 88.6% mycological 10 days after, and 67.7% clinical and 79.5 mycological 30 days after itraconazole; 64.0 clinical and 85.9% mycological 10 days after, and 62.1% clinical and 78.6 mycological 30 days after clotrimazole) with the majority of both treatment groups free from infection. A total of 69 patients reported adverse events, which were generally transient and mild. Itraconazole was more often associated with gastrointestinal or central nervous system complaints, while clotrimazole recipients more often had genitourinary symptoms. No evidence of hepatotoxicity was found. A higher incidence of relapse was noted among women on the birth control pill and among those who were symptomatic for longer than 10 days before treatment.

CONCLUSIONS: A one-day course of oral itraconazole is as effective as intravaginal clotrimazole in the treatment of acute yeast vulvovaginitis. The number of patients reporting adverse events was similar for the treatment groups, although the side effect profile differed. No hepatotoxicity was observed.

Key Words: Candida vulvovaginitis, Clotrimazole, Itraconazole

Itraconazole en traitement de courte durée de la vulvo-vaginite à *candida* : étude canadienne multicentrique

OBJECTIF : Déterminer l'efficacité clinique et mycologique de l'itraconazole par voie orale dans le traitement de la vulvo-vaginite aiguë à candida.

MODÈLE : Essai multicentrique prospectif randomisé à simple insu, portant sur 221 femmes et comparant un traitement d'un jour par itraconazole 200 mg par voie orale b.i.d. avec du clotrimazole par voie vaginale 500 mg en une seule dose.

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MESURES DES PRINCIPAUX PARAMÈTRES : Les symptômes, les signes et les résultats mycologiques ont été évalués pendant une période de jusqu'à deux mois suivant le traitement. Les réactions indésirables ont été notées et les signes d'hépatotoxicité ont été surveillés.

RÉSULTATS : Aux jours 10 et 30, suivant le traitement, les taux de guérison clinique et mycologique étaient semblables (itraconazole 61,3 % clinique et 88,6 % mycologique 10 jours après et 67,7 % clinique et 79,5 % mycologique 30 jours après; clotrimazole 64,0 % clinique et 85,9 % mycologique 10 jours après et 62,1 % clinique et 78,6 % mycologique 30 jours après), la majorité des sujets des deux groupes étant libres de toute infection. En tout, 69 patientes ont signalé des réactions indésirables qui étaient en général transitoires et légères. L'itraconazole a été plus souvent associé à des plaintes concernant l'appareil digestif ou le système nerveux central alors que les patientes ayant reçu du clotrimazole manifestaient plus souvent des symptômes génito-urinaires. Aucun signe d'hépatotoxicité n'a été noté. Une fréquence plus élevée de rechute a été notée parmi les femmes qui prenaient des contraceptifs oraux et parmi celles dont les symptômes duraient depuis plus de 10 jours avant le traitement.

CONCLUSIONS : Un traitement d'un jour par itraconazole par voie orale est aussi efficace que le clotrimazole par voie intravaginale dans le traitement de la vulvo-vaginite à levure aiguë. Le nombre de patientes ayant signalé des réactions indésirables a été semblable pour les deux groupes thérapeutiques, bien que le profil d'effets secondaires ait différé. Aucune hépatotoxicité n'a été notée.

Yeast vulvovaginitis is an extremely common gynecological problem affecting most women at some time (1). In Canada topical agents, either the polyene nystatin or an azole such as clotrimazole, are largely used in treatment.

Within the past decade orally administered and absorbable azoles have become available, initially ketoconazole, subsequently fluconazole and most recently itraconazole. The latter has excellent in vitro activity against *Candida albicans*, the usual cause of yeast vulvovaginitis, is well absorbed following oral administration with a meal, concentrates in tissues, and has a long elimination half-life and a good safety profile (2). These features suggest that it would be efficacious in the treatment of candida vulvovaginitis. This hypothesis was tested in a multicentre trial that compared oral itraconazole with vaginal clotrimazole.

PATIENTS AND METHODS

Clinical methods: Women presenting to a family physician, family planning facility or a sexually transmitted diseases clinic with symptomatic vulvovaginitis were eligible for enrolment if the following criteria were met: first, there were clinical features of yeast infection (discharge, pruritus, dysuria/dyspareunia, redness, fissuring, edema); second, the patient was symptomatic for less than 30 days and had no similar episode in the previous six months; third, the patient was between 16 and 65 years of age; and fourth, there was laboratory confirmation of infection (see 'Laboratory methods').

Study exclusion criteria were, first, evidence of a concomitant genital infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, bacterial vaginosis or treatment of such in the previous 30 days; second, any systemic antibiotic treatment within the preceding month or antifungal therapy within the past six months; third, a known immunosuppressive disorder or medical illness such as diabetes mellitus, chronic renal or hepatic disease; fourth, pregnancy or its possibility during treatment; and fifth, suspected allergy to the study drugs or to similar agents.

Eight Canadian centres enrolled patients between 1989 and 1992. A population size of 200 was the study goal. This was based upon an alpha (two-sided) set of 0.05, a power of

0.80 and 15% difference in outcomes. All study participants gave written informed consent.

Laboratory methods: At the initial visit the vaginal discharge was examined under the microscope for pseudomycelia, and to exclude *T vaginalis* and clue cells. Vaginal pH testing was not routinely carried out and, therefore, absence of clue cells and a negative 'whiff' test with 10% potassium hydroxide were used to exclude bacterial vaginosis. Eligible women then had additional testing including a vaginal culture for *C albicans*, endocervical swabs for *N gonorrhoeae* and *C trachomatis*, and blood drawn to assess beta-chorionic gonadotropin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin. Treatment was not initiated until the blood results were available and eligibility was confirmed.

Treatment: Therapy was physician-blinded. The medication and directions for use were packaged in sealed and identical containers provided by Janssen Pharmaceutica Inc. Patients received either itraconazole (Janssen Pharmaceutica Inc) four 100 mg capsules and were instructed to take two with supper and two with breakfast the following day (group I), or clotrimazole (Bayer Inc) one 500 mg suppository to be inserted at bedtime (group C). Treatment was allocated based on a predetermined randomization schema.

Monitoring: Patients kept a symptom diary which was reviewed in a three-day post-treatment telephone call and at subsequent follow-up visits. On these occasions patients were questioned about genital symptoms (discharge, pruritus, dysuria/dyspareunia) and the occurrence of side effects, and had repeat gynecological examination which involved visualization of the introitus, vagina and cervix for evidence of redness, swelling, fissuring and discharge.

Symptoms and signs were rated as none (0), mild (1), moderate (2) or severe (3). Clinical cure (responder) was defined as a lack of patient symptoms and absence of signs of infection on perineal and speculum examination.

At each follow-up visit vaginal secretions were examined microscopically for pseudomycelia and cultured for *C albicans*. A mycological cure (responder) was considered to have occurred when microscopy (wet mount/Gram stain) and culture were negative.

TABLE 1
Patient demographics

	Treatment group	
	Itraconazole (n = 106)	Clotrimazole (n = 115)
Age (years) ± SD	26.7±7.4	28.2±8.2
Weight (kg) ± SD	60.9±11.2	60.8±9.9
Caucasian (%)	95.2	93.0
Oral contraceptive use (%)	50.0	59.1
Duration of current episode (days) ± SD	9.0±6.7	9.6±8.1
Mean grouped symptom score ± SD	4.46±2.45	4.13±2.56
Mean grouped signs score ± SD	6.06±3.67	6.13±3.5

Patients' observations totalled five (itching, burning, dysuria, dyspareunia, overall rating) and physicians' observations totalled seven (external redness, swelling and fissures, internal redness, swelling and fissures, and petechiae). These numbers were added to give the grouped symptoms and grouped signs scores. None of the differences in patient demographics and baseline characteristics at baseline was statistically significant.

Patient relapse was considered to have occurred when a cleared patient's signs and symptoms recurred. Mycological relapse was considered to have occurred when microscopy and/or culture results became positive for *C albicans*.

Blood was drawn at follow-up visits to assess liver function parameters (AST, ALT and total bilirubin).

Statistical analysis: Analyses of the demographics and baseline characteristics to detect differences between the two treatment arms used Student's t test (continuous data) and Pearson's χ^2 (categorical data). Treatment outcomes, such as clinical or mycological response rates, were subjected to either Pearson's or Mantel-Haenszel χ^2 tests to detect differences between the treatment groups. The Kaplan-Meier method was used to calculate the time to clear and relapse. $P<0.05$ was considered to be statistically significant.

RESULTS

Two hundred and fifty-six patients were randomized and equally divided between the two treatment groups. Thirty-five (14%) were considered unevaluable: 22 (63%) and 13 (37%) in the I and C groups, respectively. The reasons for exclusion from the analysis and number excluded were negative pre-treatment culture for *C albicans*, 16 (11 in group I; five in group C) (46%); only screening visit data were available, 10 (six in group I; four in group C) (29%); culture was positive for *C trachomatis* or *N gonorrhoeae*, seven (five in group I; two in group C) (20%); failure to use the medication properly, two (none in group I; two in group C) (6%). Some patients were excluded for more than one reason. Thus, 221 patients were considered evaluable for the efficacy analysis and, of these, 106 (48.0%) and 115 (52.0%) were assigned to the I and C groups, respectively. Eighty-four patients, 47 from the I group and 37 from the C group, were considered premature withdrawals.

TABLE 2
Clinical and laboratory findings

	Clinical response (%)	Laboratory response (%)
First follow-up (after 10 days)		
Itraconazole (n = 106)	61.3	88.6
Clotrimazole (n = 114)	64.0	85.9
Second follow-up (after 30 days)		
Itraconazole (n = 93)	67.7	79.5
Clotrimazole (n = 103)	62.1	78.6

A clinical response indicates no symptoms or signs of infection, while a laboratory response indicates a negative wet mount/Gram stain plus culture for candida. The differences observed were not significant

The most common reasons for withdrawal were clinical relapse, infective organism (other than candida), treatment failure, loss to follow-up, patient request and adverse experiences.

The two treatment groups did not differ statistically with respect to age, weight, race, method of contraception, duration of current episode or vulvovaginal infection severity as assessed by mean grouped symptoms and signs scores (Table 1). Sexual histories were also comparable, with approximately 80% of patients currently sexually active and 95% sexually active within the preceding 12 months. Three-quarters of those currently sexually active had a single sexual partner and approximately 6% reported their partner to be symptomatic with a genital infection.

Twenty-four (22.6%) itraconazole- and 23 (20%) clotrimazole-treated patients had an episode of yeast vulvovaginitis diagnosed in the preceding six to 12 months, and of these approximately 4% of patients in each group had had two episodes in the same period.

Follow-up: Relapse rates were evaluated at day 60 for both treatment groups, and the majority of patients had a sustained response (Table 2). Mean time to relapse as calculated from patient diary data was 61.9 days for 74 I group and 54.3 days for 94 C group patients. None of these differences was statistically significant, although it was shown that women with a longer duration of current vulvovaginal yeast infection ($P=0.0003$) or who were on the birth control pill ($P=0.0270$) were more likely to relapse, irrespective of the treatment regimen received.

Mean time to mycological relapse was 56.2 days for 64 I group and 56.5 days for C group patients. The same covariate associations for relapse were also observed with respect to duration of current episode ($P=0.0023$) and birth control pill ($P=0.0035$).

Adverse events: Adverse events were reported on nonleading direct questioning of the patient or noted in the patient diary. Sixty-nine (27.0%) patients, out of all patients who entered the trial, reported at least one adverse event. Of these, 41 (32.0%) and 28 (21.9%) were in the I and C treatment groups, respectively ($P=0.0671$). Two patients experienced adverse events that caused them to withdraw from the study. Both of these patients received itraconazole. One patient reported nausea,

paraesthesia and increased appetite and the other reported severe itching in the genital area.

In total, nine patients had adverse events judged to be severe: five in the I group and four in the C group. Adverse events noted included nausea, genital pruritus, headache, anorexia and somnolence (I group) and headache, pruritus, dyspareunia and leukorrhea (C group). Only 5% of reported side effects in each treatment group were considered, in the physician's opinion, to be definitely treatment-related. Those receiving itraconazole more often complained of abdominal pain (13 in the I group, one in the C group) ($P < 0.0014$), while those treated with clotrimazole more often experienced genitourinary (insertion site pain/reaction, intermenstrual bleeding, etc) complaints (nine in group C as well as one in group I).

Few laboratory abnormalities were observed. Eight itraconazole- and seven clotrimazole-treated patients had one or more of ALT, AST and total bilirubin elevated upon enrolment. Patients with abnormal laboratory results at follow-up had initially abnormal results at baseline. Only one result was indicated by the investigator as clinically significant (in the C group) and this was a screening value. In no case were findings considered to be drug related.

DISCUSSION

It is estimated that three-quarters of the female population will suffer at least one attack of candida vulvovaginitis (1). Many treatment options have been available, but until recently all therapy has been topical. No one form of topical treatment has been shown to be clearly superior to another. Further, for patients with acute infection, short-course therapy has, in general, been found to be as efficacious as more prolonged treatment (3).

Many women, however, find topical therapy unpleasant and would prefer an oral agent (4,5). With the introduction of the oral azoles such an option now exists. Ketoconazole has been used with some success; however, the results of single-dose treatment have not been optimal (6). The present study compared one-day 400 mg oral itraconazole administered as two doses given approximately 12 h apart with single dose clotrimazole given by vaginal suppository, the latter being a standard regimen. An earlier study of itraconazole showed this short-course regimen to be as effective as more prolonged treatment with the same agent (7).

In the assessment of efficacy both the patient's and examining physician's evaluations were considered, along with laboratory evidence of candida eradication. At 10 days, approximately 60% of both itraconazole- and clotrimazole-treated patients were judged completely clear of infection clinically, although approximately 86% of patients had negative smears as well as culture for *C. albicans*. By day 30, clinical resolution was reported for 67.7% and 62.1% of I and C group patients, respectively, which was closer to the mycological response rate of 79.5% (I group) and 78.6% (C group) observed at this time. The lower clinical response rate may be attributable to the stringent definition of clinical cure (signs + symptoms = 0). It may also suggest that not all symptomatology observed was attributable to yeast infection. Certainly it

emphasizes the importance of distinguishing between clinical and laboratory outcome when comparing data from other clinical studies and in defining these parameters in precise terms. In this study we found no significant differences between the two regimens in terms of clinical or mycological response, time to resolution and relapse when patients were followed for up to 60 days post-treatment.

Recently Woolley (8) compared clotrimazole, fluconazole and itraconazole in the treatment of acute yeast vulvovaginitis. Two hundred and twenty-nine women were enrolled and follow-up was limited to 10 days after treatment. This study, like ours, found no difference in clinical/mycological cure rates between clotrimazole and itraconazole but fluconazole performed less well clinically although not mycologically. It should be noted, however, that Sobel et al (9), observing a larger group (429 patients) over a longer period (35 days), found clotrimazole and fluconazole to be equally efficacious in both parameters. This suggests that all three regimens are probably equivalent and the choice of one versus another would depend on other parameters such as cost, convenience and patient preference. The costs of drug acquisition at Victoria Hospital, London, Ontario (October 1995) were clotrimazole 100 mg vaginal tablet \$1.47; itraconazole 100 mg oral \$3.50; and fluconazole 100 mg oral \$8.91.

The incidence of reported adverse events in our study was higher for both drugs than in an earlier trial (7); however, the use of a daily diary along with nonleading direct questioning may be responsible for this finding. Furthermore, one study suggests that complaints associated with treatment are common even in those who receive placebo (10). The liver function abnormalities seen clearly preceded therapy and, indeed, resolved in many cases following treatment. Although liver function abnormalities have been reported with chronic itraconazole use (11), we observed none in 128 women who were randomized to the itraconazole limb of the study. Because of itraconazole's effect on the P-450 cytochrome enzyme system, there is the potential for interaction with a number of other therapeutic agents; however, the risk with a one-day regimen is expected to be minimal and clinically insignificant (2).

It is important to keep in mind the limitations of this study. Women with chronic symptomatology or with frequent recurrences of infection were specifically excluded, along with pregnant women or those with known immunosuppressive or metabolic disease, which are established predisposing factors for candida vulvovaginitis. In addition, the study population was almost totally Caucasian, predominantly monogamous and, although women up to age 65 years were eligible, the majority of women were premenopausal, mostly in the third decade of life. All of these factors limit the generalizability of the study results. An interesting and statistically significant finding was that women using birth control pills and those symptomatic for longer periods of time were more likely to relapse irrespective of therapeutic agent used. This observation has not been looked for or commented on by others, although Sobel et al (9) noted that women with recurrent vaginitis were more likely to fail therapy with either fluconazole or clotrimazole.

zole. Whether a more prolonged course of treatment would result in a better long term response in these groups was not addressed in the present study. Clearly this would be important to ascertain, given the general trend to short term treatment.

CONCLUSION

It was determined that short term therapy with oral itraconazole was as efficacious as intravaginal clotrimazole for both clinical and mycological outcomes. These results are similar to previously those of published trials (4,7,8) and indicate that itraconazole 400 mg in two divided doses can be considered an effective treatment for acute uncomplicated yeast vulvovaginitis.

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